Neuro-Oncology Program

The goals of the Neuro-oncology Committee are: 1) to improve duration and quality of life of brain tumor patients; 2) to assess disease and treatment-related effects on neurocognitive function and quality of life (QOL), and develop interventions; and 3), to identify prognostic and predictive variables that correlate with outcome and improve clinical trial methodology.

Capsule Summary:

For newly diagnosed GBM, the Phase I component of N057K (RT+TMZ+everolimus) is now accruing to the third dose level cohort; this trial will open to group when a Phase II dose has been established. N0874 (Phase II study of RT+TMZ + SAHA) is approved by CTEP and will open soon in cooperation with the newly formed American Brain Tumor Consortium (ABTC). N0877 (Phase II RT+ TMZ + Dasatanib vs placebo) is being revised for resubmission to CTEP. RTOG R0825 (Phase III trial of RT+TMZ + bevacizumab or placebo) has recently activated within RTOG; NCCTG has endorsed and will activate this trial soon.

For recurrent GBM, three Phase II trials are open: N0572 (sorafenib and temsirolomus); N0776 (sorafenib + bevacizumab) and N0779 (SAHA + bortezumib). N0872, a Phase II study of dasatanib + bevacizumab is under review and is expected to open later in 2009.

For grade 3 astrocytoma, two intergroup Phase III trials are opening. N0577 / CODEL study (RT vs RT+TMZ vs TMZ) is for patients with anaplastic oligodendroglioma/mixed glioma with 1p/19q deletions; this trial is approved and will activate to group approximately May 1. NCCTG will participate via CTSU in the EORTC 26053 / CATNON study (RT vs. RT+TMZ → Observation or TMZ), this trial is actively accruing in Europe and NCCTG but is not yet open in the U.S.

For low grade glioma, NCCTG will perform an intergroup study ECOG E3F05 (RT vs RT+TMZ). This study is approved by NCI and CIRB and is under final processing.

For newly diagnosed brain mets, the Phase III intergroup study N0574 (SRS vs. SRS + whole brain RT) is open.

For newly diagnosed CNS lymphoma, the intergroup study E1F05 (Rituxan + MTX/araC) is open.
Detailed Report: Cancer Treatment Trials:

**Newly Diagnosed Glioblastoma** (grade 4 astrocytoma):

**N057K**: Phase I–II evaluation of RT + TMZ followed by adjuvant TMZ + everolimus (RAD001) is activated and accruing on the Phase I to the third dose level cohort. Phase II will open after identification of the MTD

**N0874**: Phase II RT+TMZ+SAHA is a joint effort between NCCTG and the American Brain Tumor Consortium (ABTC) is approved and will open soon.

**N0877** is a Phase II randomized study of RT+TMZ+ dasatanib vs placebo. This study is being revised following NCI review and will hopefully open later this year.

**R0825** is a Phase III randomized study of RT+TMZ + avastin vs. placebo. Patients will be stratified by MGMT and gene profile status. The study activated to RTOG April 15 and is being processed for opening within NCCTG under the new Endorsement Plus program via CTSU, which allows site investigators to identify either NCCTG or RTOG for registration credit. It should be open to NCCTG within the next few months.

**N027D** “A Phase I Study of temsirolimus (CCI-779), temozolomide, and radiation in Newly Diagnosed Glioblastoma Multiforme” is open at Mayo Clinic Rochester only, and is nearing accrual goals. This study includes FDG PET pre and post treatment to identify evidence of early metabolic activity of study treatment.

**Newly Diagnosed Anaplastic Gliomas** (grade 3)

**EORTC 26053 / CATNON** is a Phase III randomized study of RT vs. RT + TMZ followed by either observation or adjuvant TMZ for patients with anaplastic gliomas that either have no or one deletion for 1p or 19q. RTOG will lead this study in the US and NCCTG will endorse the study and participate via CTSU. Patients will be stratified by MGMT status, and the study contains neurocognitive/QOL and translational components. Overall survival is the primary endpoint. This study has been open in Europe and RTOG is processing the trial for submission to NCI.

**Anaplastic Oligodendroglioma and Oligoastrocytoma**.

**NCCTG N0577 / CODEL** is a Phase III Intergroup study of RT vs RT/TMZ vs TMZ for anaplastic oligodendroglioma or mixed anaplastic glioma with combined deletions of 1p and 19q. This study was approved by NCI and CIRB, and is set to activate to Group in May. RTOG, ECOG, NCIC and EORTC will participate in the trial via CTSU. The primary endpoint for the RT vs RT/TMZ component is overall survival; a neurocognitive/clinical/radiographic endpoint is being utilized to compare the TMZ vs. RT arms. The study contains neurocognitive/QOL and translational elements.
Low Grade Glioma:

**E3F05** is an ECOG/NCCTG Phase III study for newly diagnosed high risk low-grade glioma patients, comparing RT vs RT+TMZ. The primary endpoint is 5 year survival. This study has been approved by NCI and CIRB and is being processed for activation in the near future.

Newly Diagnosed Primary CNS Lymphoma:

**E1F05** is an ECOG/NCCTG Phase II study of rituximab + chemotherapy (MTX+ vincristine+procarbazine+dex+ara-C) for newly diagnosed primary CNS lymphoma. The study is open for accrual.

Recurrent Glioblastoma and Grade 3 Anaplastic Astrocytoma:

**N0572** is the Phase II component of this study, testing the combination of Sorafenib and CCI-779 in recurrent GBM patients, remains open for accrual.

**N0776** is a Phase II study of the combination of SAHA (vorinostat) and bortezumib (PS-341) for recurrent GBM, which is open to Group for accrual.

**N0779** is a Phase II study of the combination with sorafanib and bevacizumab for recurrent GBM, and is open to Group for accrual.

**N0872** is a Phase I/II study of the combination of dasatanib and bevacizumab for recurrent GBM, is being finalized. After the determination of the MTD this study will open to Group as a Phase II.

Recurrent Oligodendroglioma and Mixed Oligoastrocytoma:

**N0272** is a Phase II trial of imatinib for recurrent oligodendroglioma/mixed glioma. Accrual has been slow but steady and N0272 remains open for to completion The group is reminded that this study is open for patients who have failed multiple (i.e., > 2) regimens for recurrence, and also for both anaplastic and low grade oligos/mixed gliomas.

CNS Metastases:

**NCCTG N0574** is a Phase III randomized trial comparing SRS to SRS + whole brain radiation for patients with 1-3 CNS metastases. The study was amended to modify the primary endpoint to neurocognitive progression, and as a result the total number of patients necessary to complete the trial was significantly diminished. The study was also amended to allow patients without controlled systemic disease to be eligible. The group is encouraged to accrue to this study to help answer this important question.

Neurobehavioral / QOL Studies
NCCTG XX09 is a study comparing citalopram to placebo for depression in patients with GBM. Members of the Neuro committee are encouraged to participate in this Cancer Control effort.

**Translational Studies**

Translational correlative studies accompany nearly all of the recent and active treatment protocols, including N0272, N0577, N027D, N0572, N0574, N057K, E3F05, R0525, N0776, N0779, N0872, N0874, and N0877. Many of the new trials include tissue analyses for prognostic factors, and even assignment of protocol based on markers at baseline. Patients eligible for N0577 and EORTC 26053 will have determinations of 1p/19q status prior to study treatment. Methylguanine methyltransferance (MGMT) gene promoter hypermethylation status, and gene profiling performed at MD Anderson will be used as stratification factors for RTOG 0825.

Quality of life and neurocognitive correlative investigations accompany many of our trials, including N0272, N0776, N0879, N0572, N0577, N0574, E3F05, and R0825.

The group members are again to be congratulated on a superb job of acquiring and mailing of tissue and blood specimens obtained from patients on our trials who have provided consent for the translational tissue correlative analyses. Many of these correlative studies provide the scientific rationale for design of our clinical trials, and support the overall goals of the Neuro-oncology committee. We recognize that this component takes time from busy practices, and the NCCTG is very appreciative of your efforts.

**Database Studies.**

N047D “compared different potential outcome endpoints for determination of treatment efficacy in our clinical trials, and found that progression free survival at 6 months (PFS6) correlated reasonably with a survival endpoint (OS12), confirming its usefulness as the primary endpoint in our recurrent disease trials. A manuscript has been published. 94-72-53, "Diagnostic and Prognostic Markers in Low-Grade Gliomas" and 94-72-52, "Diagnostic and Prognostic Markers in Anaplastic Astrocytoma and Anaplastic Oligoastrocytoma" continues to mature and collect specimens, for which credit is given. NCCTG N0475 found that patients receiving EIAC at baseline in three of our up-front GBM studies paradoxically correlated with longer survivals, and a manuscript has been submitted. A recent cooperative effort between NCCTG and UCSF has evaluated prognostic variables in Recurrent GBM trials.
**Recently Completed Studies – Update**

**RTOG 0525**, the intergroup effort with NCCTG, NCIC, and EORTC reached accrual in June, 2008, and data is maturing. This Phase III study for newly diagnosed GBM compared standard adjuvant TMZ to dose dense TMZ after conventional chemoradiation with TMZ.

**NCCTG Neuro-Oncology Program Accepted Manuscripts and Abstracts 2009:**

**Manuscripts:**


Jaeckle K, Ballman K, Furth A, Buckner J: Correlation Of Enzyme-Inducing Anticonvulsant Use With Outcome Of Glioblastoma Patients. (Submitted)

**ASCO abstracts:**
